

REMARKS

Applicants thank the Examiner for extending the courtesy of a telephone interview with the undersigned on July 2, 2003.

Applicants gratefully acknowledge the Examiner's remarks in the May 20, 2003 Office Action that References AW, BQ and CM of the Information Disclosure Statement have been considered and that the rejection of claim 8 under 35 U.S.C. §112, second paragraph has been withdrawn.

The Rejections under 35 U.S.C. §103

The Examiner has rejected claims 1, 3-7, 9, 11, 14-17 and 21-40 as allegedly being unpatentable over Kirkwood et al., J. Clin. Oncol. 14(1): 7-17, 1996 (hereafter "Kirkwood") in view of Gilbert et al., United States Patent 5,951,974 (hereafter "Gilbert"), in view of Glue et al., United States Patent 5,908,621 (hereafter "Glue"), and further in view of Talpaz et al., Blood 92(10): 251a, 1998 (hereafter "Talpaz"). The Examiner states that claims 1, 3-7, 9, 11 and 14-17 are rejected for reasons of record and has applied the same rejection to added claims 21-40.

The Examiner has rejected claims 1, 3-7, 10, 11, 13 and 14 as allegedly being unpatentable over Creagan et al., J. Clin. Oncol. 13(11): 2776-2783, 1995 (hereafter "Creagan") in view of Gilbert, and further in view of Glue for reasons of record.

In response to applicants' arguments that the art of treating melanoma with pegylated interferon alpha was unpredictable at the time of filing, the Examiner states that either of Gilbert or Glue teaches that methods for arriving

at optimal dosages of pegylated interferon alpha are known in the art. The Examiner further states that applicant has failed to provide evidence that the art of arriving at optimal doses of pegylated interferon alpha for melanoma treatment was unpredictable. Applicants respectfully traverse.

Applicants have provided herewith a Declaration Under 37 C.F.R. §1.132 of Craig Tendler, M.D. (hereafter "the Tendler declaration"). The Tendler declaration explains that the claimed methods are not obvious in view of the cited references because the cited references are not predictive of the safe and effective use of pegylated interferon in the treatment of melanoma. See ¶ 4 of the Tendler declaration.

Contrary to the Examiner's assertion, the claimed invention is not obvious because one having ordinary skill in the art would not have had a reasonable expectation of success at the time the invention was made that one could substitute the pegylated interferon alpha of Gilbert, for the unconjugated interferon alpha in the methods of Kirkwood or Creagan because these two drugs differ from each other in important ways. Specifically, unpegylated interferon alpha and pegylated interferon alpha are structurally and functionally distinct drugs with substantially different pharmacokinetic properties. See ¶¶ 5-6 of the Tendler declaration. For example, administration of pegylated interferon alpha to a patient provides *lower* peak plasma levels but *prolonged* total dose exposure of interferon alpha activity as compared to administration of unconjugated interferon alpha. See ¶ 6 of the Tendler declaration. These differences in pharmacokinetic properties are critical because a particular pharmacokinetic parameter, such as a patient's total exposure to a drug (AUC)

or the peak plasma level of the drug ( $C_{max}$ ), is often essential for successfully treating a specific disease. See ¶ 7 of the Tendler declaration. In Dr. Tendler's opinion, the efficacy of pegylated interferon alpha for treating melanoma could not have been reasonably predicted based upon the efficacy of unconjugated interferon alpha in treating the disease because these two drugs have significantly different physical and pharmacokinetic properties. See ¶ 8 of the Tendler declaration.

Glue, which states that pegylated interferon alpha may be used to treat hepatitis C, and Tal Paz, which states that pegylated interferon alpha may be used to treat chronic myelogenous leukemia (CML), do not cure this defect. In Dr. Tendler's opinion, the efficacy of a particular drug could not have been predicted based upon treatment of a different disease with the same drug because hepatitis C and CML have different etiologies and effects than melanoma. See ¶ 9 of the Tendler declaration. In addition, using pegylated interferon alpha to treat hepatitis C would not have been predictive of its efficacy in treating melanoma because the anti-viral mechanism of interferon alpha may be different from its anti-melanoma mechanism. See ¶ 9 of the Tendler declaration.

The claimed invention is also not obvious over the cited references because one having ordinary skill in the art would not have had a reasonable expectation, at the time the invention was made, that administration of pegylated interferon alpha would be safe at the doses required to treat melanoma. Administration of pegylated interferon alpha results in more prolonged total drug exposures in patients, which might cause side effects

severe enough that treatment would have to be discontinued. See ¶ 10 of the Tendler declaration. Further, contrary to the Examiner's assertion that pegylation of interferon alpha would allow the administration of higher doses of the drug, it was recognized in the art that side effects from interferon alpha could result in treatment being halted. See ¶ 10 of the Tendler declaration, citing Gilbert, col. 11, lines 22-25.

The safe treatment of hepatitis C and CML, as disclosed by Glue and TalpaZ, is also not predictive of the drug's safety in treating melanoma. One skilled in the art would have expected that higher doses of pegylated interferon alpha might have to be administered to treat melanoma compared to the doses used for hepatitis C, which would have resulted in a greater total drug exposure and a higher risk of unmanageable side effects. See ¶ 11 of the Tendler declaration. In addition, an artisan of ordinary skill would not have been able to predict whether pegylated interferon alpha could be safely used to treat melanoma based upon its safe use in CML because the artisan would have recognized that there might be different drug tolerability profiles for melanoma and CML. See ¶ 11 of the Tendler declaration. In fact, Schering-Plough conducted Phase I clinical studies to determine the safety profiles of pegylated interferon alpha for both solid tumors, such as melanoma, and hematologic malignancies, such as CML. See ¶ 11 of the Tendler declaration.

For the reasons provided above, it was unpredictable at the time the invention was made whether pegylated interferon alpha could be substituted for unconjugated interferon alpha to safely and efficaciously treat melanoma. Due to this unpredictability, one having ordinary skill in the art would not have

had a reasonable expectation that the cited references could have been successfully modified as asserted by the Examiner, which is required for a finding of obviousness. See, e.g., Manual of Patent Examining Procedure 2143.03.

*Conclusion*

Applicants request that the Examiner consider the foregoing remarks, allow the pending claims and pass this application to issue.

If the Examiner should have any questions regarding this response or application, she is encouraged to contact the undersigned agent.

Respectfully submitted,

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